RESEARCH ARTICLE

Age-Related Differences in the Association between REM Sleep and the Polygenic Risk for Parkinson's Disease

Puneet Talwar, PhD,[1] Nasrin Mortazavi, PhD,[1] Ekaterina Koshmanova, PhD,[1] Vincenzo Muto, PhD,[1] Aurora Gasparello, MSc,[1] Christian Degueldre, MSc,[1] Christian Berthomier, PhD,[2] Fabienne Collette, PhD,[1] Christine Bastin, PhD,[1] Christophe Phillips, PhD,[1] Pierre Maquet, PhD,[1,3] Mikhail Zubkov, PhD,[1] and Gilles Vandewalle, PhD[1]

Objective: Parkinson's disease (PD) is one of the rare diseases in which sleep alteration is a true marker of disease outcome. Yet, how the association between sleep and PD emerges over the healthy lifetime is not established. We examined the association between the polygenic risk score (PRS) for PD and the variability in the electrophysiology of rapid eye movement (REM) sleep in 433 younger (18–31 years) healthy individuals and 85 late-midlife (50–69 years) healthy individuals.
Methods: In this prospective cross-sectional study, in-lab electroencephalography recordings of sleep were recorded to extract REM sleep metrics. PRS was computed using SBayesR approach.
Results: Generalized additive model for location, scale, and shape analysis showed significant association of REM duration ($p_{corrected} = 0.03$) and theta energy in REM ($p_{corrected} = 0.004$) with PRS for PD in interaction with the age group. In the younger subsample, REM duration and theta energy were positively associated with PD PRS. In contrast, in the late-midlife subsample, the same associations were negative (although only qualitatively for REM theta energy) and may differ between men and women.
Interpretation: REM sleep is associated with the PRS for PD in early adulthood, 2 to 5 decades before typical symptoms onset. The association changes from positive in younger individuals, presumably free of alpha-synuclein, to negative in late-midlife individuals, possibly because of the progressive presence of alpha-synuclein aggregates or of the repeated increased oxidative metabolism imposed by REM sleep. Our findings may unravel core associations between PD and sleep and may contribute to novel intervention targets to prevent or delay PD.

ANN NEUROL 2025;00:1–13

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder. The global burden of PD has surged from 2.5 million people in the 1990s to 8.5 million today, a trend expected to continue in the next decades.[1] The incidence of PD increases with age and is higher in men than women.[2] PD is characterized by a heterogeneous pathology, with significant variations in clinical manifestations—with both motor and non-motor symptoms and signs, including during sleep—as well as in disease progression and responses to treatment.[2,3] The neuropathological hallmark of PD consists of conspicuous lesions in the substantia nigra (SN), a major dopaminergic nucleus forming the nigrostriatal pathway,[4] in the form of intracellular inclusions of alpha-synuclein known as Lewy bodies, accumulation of neuromelanin and iron, and neuronal loss.

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.78112

Received Feb 10, 2025, and in revised form Oct 24, 2025. Accepted for publication Nov 10, 2025.

Address correspondence to Dr. Talwar and Prof. Vandewalle, GIGA-Institute, CRC-Human Imaging, Bâtiment B30, Université de Liège, 4000 Liège, Belgium. E-mail: ptalwar@uliege.be and gilles.vandewalle@uliege.be

From the [1]GIGA-Institute, CRC-Human Imaging, University of Liège, Belgium; [2]Physip, Paris, France; and [3]Department of Neurology, CHU of Liège, Liège, Belgium

Additional supporting information can be found in the online version of this article.

Currently, PD remains a clinical diagnosis, because no laboratory or neuroimaging biomarkers can definitively confirm the disease. Existing pharmacological treatments primarily address motor symptoms without halting the underlying neurodegenerative processes.[5] The challenge in developing neuroprotective therapies is compounded by the extensive neurodegeneration present by the time motor symptoms and PD diagnosis occur. Therefore, early identification of presymptomatic PD, or of high risk for PD, is a critical medical need to develop effective neuroprotective strategies, delay, or prevent the symptomatic stage of the disease.

Notably, excessive daytime sleepiness significantly increases the risk of developing PD.[6] Critically, the majority of individuals with idiopathic rapid eye movement (REM) sleep behavior disorder (RBD)—characterized by loss of normal atonia and vigorous movements during REM sleep—progress to PD or cognitive impairment within 10 to 15 years, making RBD a prominent sleep-related risk factor for PD.[6] The progressive disruption of REM/non-REM (NREM) sleep transitions in idiopathic RBD and PD likely reflects the early involvement of subcortical regions, such as the locus coeruleus (LC).[6–8] The literature highlights a bidirectional detrimental relationship between sleep alterations and neurodegeneration, including in PD.[9] The recently identified glymphatic system, which is proposed to be active during sleep and suppressed by LC noradrenaline, appears crucial for alpha-synuclein clearance as its dysfunction seem to exacerbate alpha-synuclein accumulation.[6,10] Sleep alterations, in REM sleep, may, therefore, not only provide early means to assess the risk for developing PD, but may also provide novel intervention targets (as one can act on sleep). However, which key features of sleep should be monitored is not established.

Although monogenic forms account for 3 to 5% of PD cases, recent genome-wide association studies (GWAS) indicate that idiopathic sporadic PD is highly polygenic.[11,12] Ninety genetic risk variants collectively account for 16 to 36% of the heritable risk of non-monogenic PD.[3] Consistent with the common disease-common variant hypothesis, PD genetic risk results from the synergistic effect of numerous common low-risk variants—in addition to environmental influences. Polygenic risk scores (PRS), derived from GWAS, hold promise for predicting and stratifying PD risk in asymptomatic individuals and already provide a critical tool to investigate the neurobiology of the disease in individuals of any age (ie, before PD hallmarks can be detected and free from disease co-morbidity).[12] In recent years, PRS for PD has been associated with olfactory impairment,[13] retinal structural integrity,[14] and cognitive deficits.[15] In this cross-sectional study, we aimed to investigate the relationship between PRS for PD and REM sleep metrics in healthy young and late-midlife individuals. We analyzed key REM sleep characteristics-related to PD pathophysiology, including metrics associated with REM sleep duration, intensity, and continuity.[16] Although the literature on the associations between sleep metrics and PD PRS are scarce, we anticipated that associations would be different in the two age groups based on the age-related changes in brain integrity.

Results

In the present study, we collected the habitual night time sleep of 518 healthy individuals under electroencephalography (EEG) (Table 1), in two subsample of younger (18–31 years; n = 433; 44 women) and late-midlife (50–69 years; n = 85; 58 women) collected from seven previous multi-modal cross-sectional projects.[17–19] We quantified four REM sleep metrics based on their potential association with PD: (1) REM duration, (2) REM latency, (3) number of arousals during REM sleep (to characterize sleep continuity[20]), and (4) REM theta energy (i.e., the cumulated theta power during REM sleep), which is associated with REMS intensity over its most typical oscillatory activity.[20] By a priori selecting variables of interest, we reduced the multiple comparison burden. We further used the summary statistics of one of the largest PD-GWAS available to date (n = 482,730)[21] to compute individual PRS for PD in our sample—based on DNA extracted from blood samples—and related these to sleep EEG characteristics. The overview of the study design is provided in Figure 1.

Associations between REM Sleep Metrics and Age

We first assessed the differences between age groups and REM sleep metrics of interest using boxplots and *t* test (Fig 2 and Table 1). All four sleep metrics were significantly lower in the late-midlife subgroup as compared to the young subgroup ($p < 0.001$), which was expected based on previous literature, except for the number of REM arousals, has previously been reported to increase significantly[22,23]

Associations between Polygenic Risk for PD with REM Sleep Duration and Intensity

Our statistical analyses consisted of a generalized additive model for location, scale, and shape (GAMLSS), which is a flexible distributional regression approach and is considered as an improvement and extension to the generalized linear models (GLM).[24] Our primary GAMLSS regression analyses included each of the four sleep metrics of interest and PRS for PD with the age group included as interaction variable with PRS. The GAMLSS with REM

TABLE 1. Characteristics for the Total Sample as Well as Young and Late-Midlife Subgroups

Characteristic	All	Young mean (SD)	Late-midlife mean (SD)	p[a]
Sample size (n)	518	433	85	
Sex (M)	80.31%	89.84%	31.76%	**<0.001**
Age (yr)	28.17 (14.09)	22.10 (2.69)	59.09 (5.26)	**<0.001**
BMI ($kg*m^{-2}$)	22.55 (2.61)	22.11 (2.32)	24.82 (2.85)	**<0.001**
Anxiety[b]	2.67 (3.10)	2.64 (3.16)	2.78 (2.86)	0.7
Mood[b]	3.29 (3.77)	2.91 (3.41)	4.85 (4.66)	**<0.001**
Sleep quality[c]	3.71 (2.08)	3.41 (1.72)	4.89 (2.86)	**<0.001**
Daytime sleepiness[c]	5.95 (3.62)	5.91 (3.53)	6.13 (3.98)	0.6
Chronotype[c]	50.87 (8.35)	50.21 (8.35)	53.49 (7.87)	**<0.001**
Total sleep time (min)	439.30 (47.11)	448.65 (42.39)	391.65 (40.88)	**<0.001**
Sleep onset latency (min)	15.87 (11.58)	16.41 (11.68)	13.12 (10.74)	**0.015**
REM duration (min)	114.89 (28.55)	119.14 (26.46)	93.23 (29.17)	**<0.001**
REM percentage (%)	26.01 (5.54)	26.47 (5.10)	23.65 (6.93)	**0.001**
REM arousal (n)	45.83 (24.18)	51.12 (22.36)	18.89 (12.13)	**<0.001**
REM latency (min)	92.04 (42.89)	93.65 (41.38)	83.85 (49.33)	**<0.001**
REM delta power (0.5–4Hz) (μV^2)	66,706 (69,597)	72,453 (72,690)	37,428 (40,005)	**<0.001**
REM theta power (4–8Hz) (μV^2)	7,305 (5,273)	7,885 (5,425)	4,354 (3,039)	**<0.001**
REM alpha power (8.25–12Hz) (μV^2)	4,192 (3,309)	4,455 (3,426)	2,850 (2,202)	**<0.001**
REM sigma power (12.25–16Hz) (μV^2)	1,287 (885)	1,376 (919)	832 (476)	**<0.001**
NREM slow wave energy (μV^2)	164,620 (163,436)	180,901 (171,319)	81,686 (71,642)	**<0.001**

Sleep quality was assessed by the Pittsburgh Sleep Quality index; daytime sleepiness was measured by the Epworth Sleepiness Scale; chronotype was assessed by the Morningness-Eveningness Questionnaire; anxiety was estimated by the Beck Anxiety Inventory; mood was estimated by the 21-item Beck Depression Inventory II; and total sleep time was extracted from polysomnography recordings. The data for [b]anxiety (n = 428), [b]mood (n = 428), [c]sleep quality (n = 425), [c]daytime sleepiness (n = 425), and [c]chronotype (n = 425) excludes some young participant subsample because of unavailability. p-values less than 0.05 are higlighted in bold.

[a]Pearson's chi-squared test; Welch two sample t test between young and late-midlife group.

BMI = body mass index; M = men; min = minute; NREM = non-rapid eye movment; REM = rapid eye movment; SD = standard deviation; yr = year.

duration ($p = 0.016$, $p_{corrected} = 0.03$) and theta energy in REM ($p = 0.001$, $p_{corrected} = 0.004$) as dependent variables yielded significant interaction between PD PRS and the age group after controlling for sex, body mass index (BMI), and total sleep time (TST) or REM duration (Table 2; Fig S1 for display). REM latency and arousal in REM did not, however, reveal significant associations with PRS for PD (Table 2).

To gain insight into the interactions, we split our sample into the young (n = 433) and late-midlife (n = 85) subsamples and recomputed post hoc GAMLSS in each subsample (see Table 1 for demographic and sleep metrics in each subgroup). We found that although the association was significantly positive in the younger subsample for REM duration ($p = 0.014$; ie, higher REM duration is related to higher PD PRS) the association was significantly negative in the late-midlife subsamples ($p = 0.02$) (Table 3, Fig 3A). In the young subsample, GAMLSS yielded no sex-specific association for REM duration with PD PRS (Table S1 and Fig S2A). However, when sex was included in the GAMLSS model including the late-midlife subsample, it yielded significant sex-by-PRS interaction ($p = 0.03$) with negative and positive links, respectively, in men and women (Table S1) with

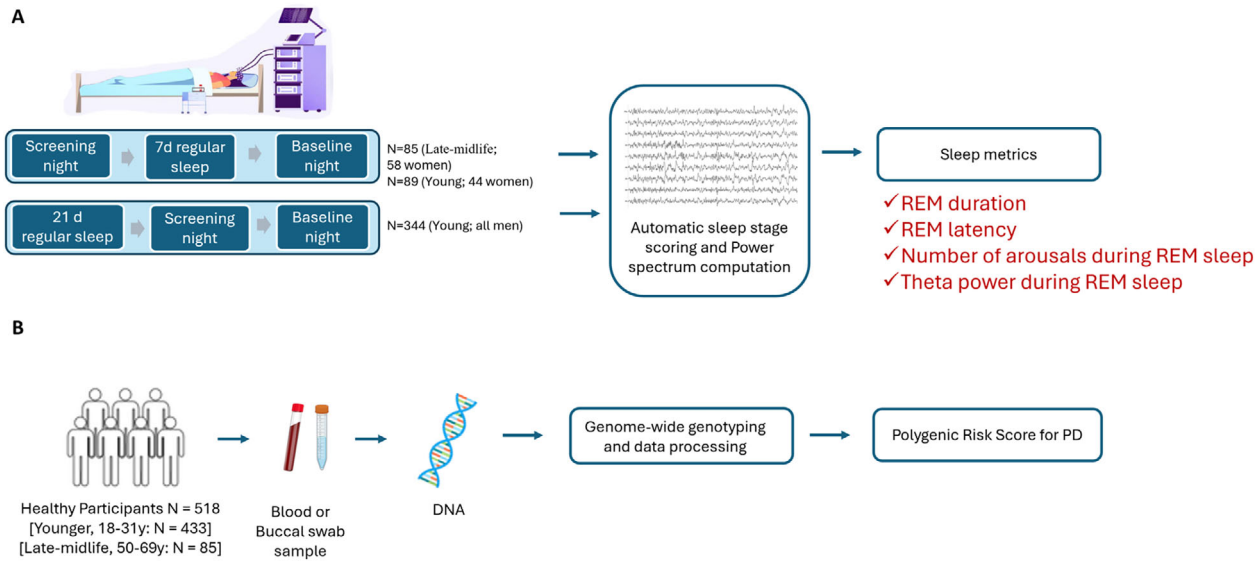

FIGURE 1: Overview of the study design: (A) In-lab recordings of habitual sleep to extract rapid eye movement (REM) sleep macrostructure and microstructure metrics. (B) Parkinson's disease (PD) polygenic risk score (PRS) computation using available genome-wide association study (GWAS) data and DNA extracted from blood sample and PD summary statistics.

significant association only with men for REM duration ($p = 0.005$) (Table S2, Fig 4A, C). These findings suggest that REM duration is associated with PD PRS in an age and possibly sex dependent manner.

The GAMLSS per age subgroup further showed that the significant association between REM theta energy and PRS for PD was positive in the younger subsample ($p = 0.012$; ie, higher REM intensity is related to higher PD risk) whereas, although it was negative, it was not significant as a main effect in the late-midlife subsample and only reach statistical trend values ($p = 0.07$) (Table 3, see Fig 3B). Moreover, in contrast to REM duration, including

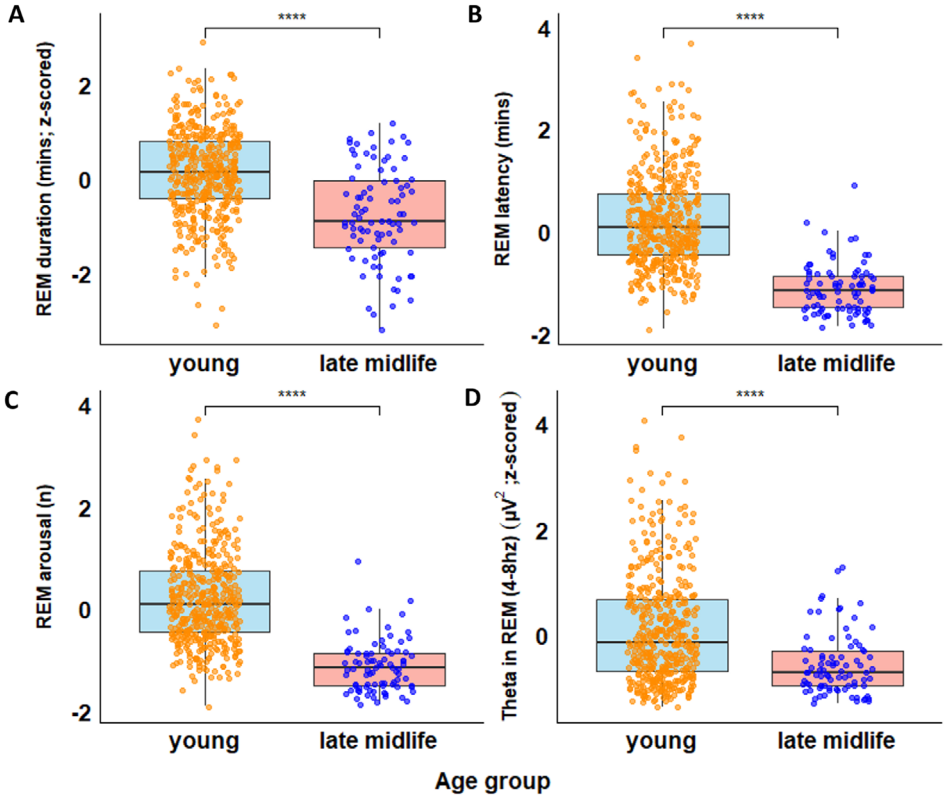

FIGURE 2: The boxplots for four sleep metrics (A–D) during baseline night and age groups (young and late-midlife) with *t* tests are reported. The sleep metrics were significantly higher in younger subgroup as compared to the late midlife group. **p* value <0.05; ***p* value <0.01; ****p* value <0.001.

TABLE 2. Results Derived from Regression Analysis When Testing for Associations between Sleep Parameters and PRS Values Computed for Parkinson's Disease RISK with Age Group as an Interacting Variable (n = 518)

	REMS duration		REMS theta power		REMS latency		REMS arousal	
Sleep parameters	**Estimate [95% CI]**	***p***	**Estimate [95% CI]**	***p***	**Estimate [95% CI]**	***p***	**Estimate [95% CI]**	***p***
PRS × age group	0.01 [0.00–0.02]	**0.016**	0.04 [0.02–0.06]	**0.001**	−0.31 [−1.16 to 0.54]	0.477	0.01 [−0.00 to 0.03]	0.086
PRS[a]	−0.01 [−0.01 to 0.00]	0.075	−0.03 [−0.05, −0.01]	**0.014**	0.15 [−0.67 to 0.96]	0.725	−0.01 [−0.003 to 0.00]	0.076
Age group	−0.01 [−0.08 to 0.06]	0.847	0.41 [0.17–0.64]	**0.001**	4.98 [−2.93 to 12.90]	0.216	0.62 [0.48–0.76]	**<0.001**
Sex	0.01 [−0.04 to 0.06]	0.665	−0.08 [−0.24 to 0.09]	0.346	3.59 [−2.75 to 9.94]	0.266	0.05 [−0.05 to 0.16]	0.302
BMI	0.003 [−0.00 to 0.01]	0.434	0.02 [−0.01 to 0.04]	0.165	0.29 [−0.66 to 1.23]	0.552	−0.01 [−0.02 to 0.00]	0.176
TST	0.003 [0.00– 0.00]	**<0.001**	0.001 [0.00–0.00]	**0.030**	0.05 [−0.00 to 0.10]	0.052	–	–
REM duration	–	–	–	–	–	–	0.01 [0.01–0.01]	**<0.001**

Regression coefficients (log scale) with 95% CI are shown. *p*-values less than 0.05 are higlighted in bold.
[a]PRS was computed for SNP reaching *p*-value threshold of 1×10^{-8} to restrict the number of SNPs included in the PRS estimation.
BMI = body mass index; CI = confidence interval; PRS = polygenic risk score; REMS = rapid eye movement sleep.

sex in the GAMLSS of the young and late-midlife subsample did not reveal sex or sex-by-PRS interactions (Table S1, see Fig 4B, D). Therefore, as with REM duration, REM intensity as measured by REM theta energy is associated with PD PRS in an age dependent manner with the direction of association changing with age.

Specificity—Association with Other Sleep Metrics

To assess the robustness of our findings, we recomputed the PRS for PD using a larger set of common variants. The GAMLSS analysis, using REM duration and theta energy in REM, yielded comparable statistical results, including slightly more variants, but not many more nor all genetic variants examined (Fig S2), which supports the need for a narrow/specific PRS for PD for associations to emerge. In addition, there was no association with a polygenic prediction of an individual physical trait with which REM sleep is not expected to be associated, such as height, showing that our results cannot be obtained with any polygenic computations (Fig S3).

To further ascertain specificity of our findings, we considered additional sleep metrics: (1) REM percentage,

TABLE 3. Results Derived from Regression Analysis When Testing for Associations between Sleep Parameters and PRS Values Computed for Parkinson's Disease Risk in Healthy Younger (n = 345) and Late-Midlife Subsample (n = 85).

	Young				Late-midlife			
	REMS duration		REMS theta energy[a]		REMS duration		REMS theta energy	
Sleep parameters	**Estimate [95% CI]**	***p***	**Estimate [95% CI]**	***p***	**Estimate [95% CI]**	***p***	**Estimate [95% CI]**	***p***
PRS[b]	0.35 [0.07–0.63]	**0.014**	0.01 [0.00–0.02]	**0.012**	−0.01 [−0.01 to 0.00]	**0.015**	−0.02 [−0.04 to 0.00]	0.069
Age	0.62 [−0.11 to 1.35]	0.096	−0.03 [−0.06 to −0.01]	**0.004**	−0.01 [−0.02 to −0.00]	**0.008**	−0.40 [−0.06 to −0.01]	**0.002**
BMI	0.59 [−0.27 to 1.46]	0.180	0.03 [0.00–0.05]	**0.035**	0.003 [−0.00 to 0.02]	0.720	−0.02 [−0.06 to 0.03]	0.536
TST	0.34 [0.30–0.38]	**<0.001**	0.001 [−0.00 to 0.00]	0.254	0.003 [0.00–0.00]	**<0.001**	0.004 [0.00–0.01]	**0.036**
Sex	6.29 [0.11–12.47]	**0.046**	0.09 [−0.11 to 0.29]	0.363	0.077 [0.04–0.17]	0.111	0.37 [0.08–0.66]	**0.012**

p-values less than 0.05 are higlighted in bold.
[a]REM theta energy is computed for 4–8Hz.
[b]PRS was computed for SNP reaching *p*-value threshold of 1×10^{-8} to restrict the number of SNPs included in the PRS estimation.
BMI = body mass index; CI = confidence interval; PRS = polygenic risk score; REMS = rapid eye movement sleep.

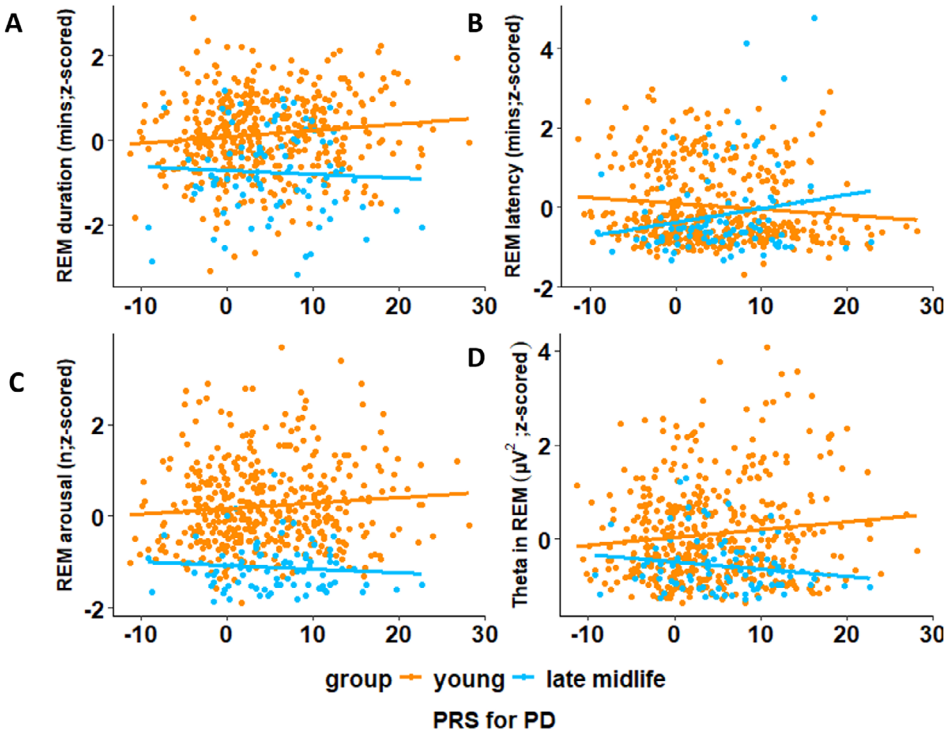

FIGURE 3: Age-related associations between polygenic risk score (PRS) for Parkinson's disease (PD) and baseline night sleep metrics for young and late-midlife subsamples (A–D). The association between (A) rapid eye movement (REM) duration and (D) theta in REM during baseline night and PD PRS were significant. Refer to main text Table 3 for complete statistical outputs of generalized additive models for location, scale, and shape (GAMLSS).

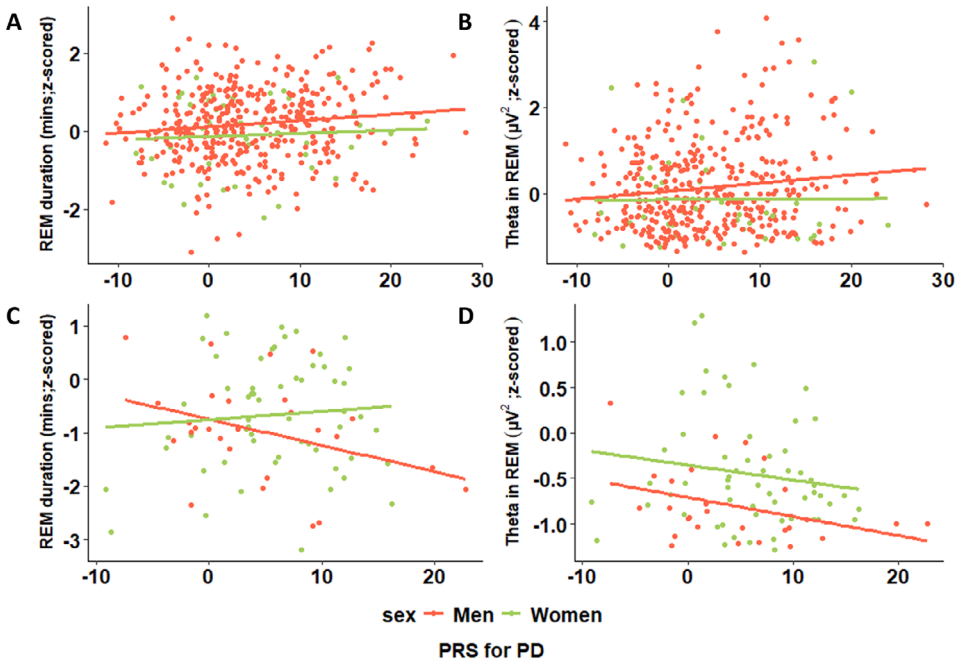

FIGURE 4: Sex-specific associations between polygenic risk score (PRS) for Parkinson's disease (PD) and baseline night sleep metrics for the young and late-midlife subsamples. In the young subsample (upper panel), generalized additive model for location, scale, and shape (GAMLSS) yielded no sex-specific association for (A) rapid eye movement (REM) duration and (B) theta in REM with PD PRS. In the late-midlife subgroup (lower panel), GAMLSS yielded significant sex-specific association for (C) REM duration with PD PRS but not for (D) theta in REM. Refer to Tables S1 and S2 for complete statistical outputs of GAMLSSs.

(2) REM delta energy, (3) REM alpha energy, (4) REM sigma energy, (5) and slow wave energy (SWE) during NREM sleep (see Methods) (Fig S4). GAMLSS analyses over the entire sample for each of these metrics yielded significant age-group by PRS for PD interaction for REM sleep percentage ($p < 0.001$) while controlling for BMI and REM duration (see Methods) (Table S3). These findings substantiate the previous results with REM duration. GAMLSS with REM delta energy, REM alpha energy, REM sigma energy, or SWE in NREM sleep showed no statistically significant association. GAMLSS per subgroup yielded similar findings for REM percentage as for the primary analysis on REM duration (Fig S5).

Discussion

Although it is well accepted that sleep is altered over PD neuropathology—with RBD almost inescapably predicting the future development of parkinsonism[6]—how the association between REM sleep and PD emerges over the lifetime is not established. Here, we find that the polygenic liability, or PRS, for PD is related to REM sleep metrics—mainly REM duration and theta energy in REM. The associations were isolated in healthy young adults 31 years old or less (ie, 2–5 decades before typical age of diagnosis) as well as in healthy late-middle age individuals 50 to 69 years. In the younger subsample, higher PRS for PD was associated with longer REM sleep duration and more intense REM sleep, as assessed by the overnight REM theta energy. By contrast, higher PRS for PD was correlated with shorter REM sleep duration, potentially specifically in men, and was qualitatively—although not statistically—associated with lower REM theta energy. The negative control analysis, using polygenic prediction of height, together with the fact that no association was found between PRS for PD and SWE or other frequency bands of REM sleep (except for delta energy), supports that the associations are stronger and/or specific to REM sleep duration and theta energy. The effect sizes we uncover are small, as in any such studies, yet their cumulative effect over the years could have important implications underlying a true contribution of sleep to PD neurobiology. In addition, the associations are found based on electrophysiology measures of sleep, which contrasts to prior studies that could only access coarser non-electrophysiological phenotyping consisting of, for example, sleep questionnaires or actigraphy alone.[25] These findings add to the current literature and may isolate the earliest and potentially core links between REM sleep- and PD-related biology.

Sleep disturbances often precede, by decades, the onset of motor symptoms in PD.[26] Our findings suggest that these alterations may initially manifest as prolonged overnight REM sleep and increased REM theta energy, which reflects the cumulative overnight power of the characteristic oscillatory activity of REM sleep. The somewhat stronger initial manifestation of REM sleep could suggest that the biology of prodromal PD leads to larger capacity for REM sleep-related processes such as memory consolidation, emotional processing, brain development, and/or dreaming[27] in those young adults with higher PD genetic liability. The biology of individuals with higher PRS for PD may lead to a stronger expression of REM, inherently—for an equivalent brain function during wakefulness—or in response to wakeful events previously experienced by the young individuals. Both options could be tested by linking electrophysiology metrics acquired during wakefulness to PRS for PD in young adult individuals. One could further test whether the PRS-for-PD–dependent manifestation of REM sleep is associated with difference in sleep-dependent memory consolidation or emotional processing.

Our results further support that later over the lifetime, while still healthy, the same associations switch to a shorter REM sleep duration and a lower REM theta energy in those with a higher genetic liability for PD. This is in line with observations that PD patients present reduced REM sleep duration.[28] In a longitudinal study involving 2,770 healthy late-midlife men, lower REM percentages were found to be associated with an increased risk of developing PD.[29] It does not match, however, the report that patients with PD-RBD may exhibit higher theta spectral energy during REM sleep[30] and that PD patients typically show a sustained increase in high-theta/alpha frequencies (7.8–10.5Hz) early in the sleep period.[31]

The reasons for the opposite age-related associations cannot be identified through our cross-sectional study. A first potential explanation may, however, be related to the high oxidative metabolism and catecholamine activity imposed by REM sleep.[32] Small structures of the brainstem such as the SN and LC are known to be particularly sensitive to oxidative insult and high cytosolic catecholamine concentration. This would be the reason why both structures show progressive high level of neuromelanin over the lifespan because it is considered that neuromelanin serves to shield the cells from toxic effects of redox active metals, toxins, and excess of cytosolic catecholamines.[33] The LC is a nucleus crucial for the transitions between NREM and REM sleep,[34] whereas dysfunction and degeneration of noradrenergic neurons in the LC are linked to RBD[35] and reduced arousal. The SN also contributes to REM regulation[36] and is central to PD motor symptoms.[37] We speculate, therefore, that those

young individuals with higher PRS that show high REM duration and intensity based on our data, would show a quicker alteration of structures, such as the SN and LC, leading to progressive reduction in REM duration and intensity.

A second plausible explanation, which is not mutually exclusive with the first one, is that the opposite age-related association in REM sleep and PRS association may be because of the progressive accumulation of alpha-synuclein and Lewy bodies, which is presumably quicker in individuals with higher PRS for PD. The earliest brain α-synuclein deposits appear long before the onset of motor symptoms, primarily in brainstem structures of the extended medulla and pons (Braak stages 1 and 2[38]), including LC. Likewise, ventral tegmental area (VTA) dopaminergic neurons lesion in rats reduced total NREM and REM sleep duration during the sleep phase.[39] We posit, therefore, that alpha-synuclein aggregates in the LC, and maybe in the VTA, and in the SN, contributes to the association we find between REM duration and PRS for PD.

The hippocampus is the source of ripple oscillations that are essential to the interplay between the limbic system, the thalamus, and the cortex that contributes to memory consolidation.[40] Ripples cannot be directly detected per se on the EEG, which arises mostly from the activity of cortical neurons, but they contribute to theta cortical oscillations in the cortex.[41] In addition, lesions of the VTA dopaminergic neurons in rats were found to lead to suppression of EEG theta rhythm frequency during both wakefulness and REM sleep, suggesting that midbrain dopaminergic neurons contribute to hippocampal theta activity.[42] The changes in theta oscillation energy could, therefore, arise from the putative alpha-synuclein aggregates in the hippocampus or in the VTA.

In addition, later, when alpha-synuclein or neuromelanin is eventually shed in the extracellular space on neuronal death, the neuroinflammation response and/or modulation of glymphatic system by sleep state could further influence PD process.[10,33] It is, therefore, also possible that early REM sleep alteration contributes to the neurobiology of PD and to the progressive increase in oxidative insults and misfolded alpha-synuclein burden,[6,10] which would in turns alter sleep regulation and oscillations.

The cross-sectional nature of our study precludes causal inferences and is not its only limitation. The exclusion criteria for participant selection were rigorous and not common for large genetic studies. As poor sleep, daytime sleepiness, and REM without atonia (RSWA) can occur in the prodromal phase of PD, by excluding such participants we excluded some of the highest-risk individuals, especially among older participants. The goal of the study was to examine REM sleep and PD biology in the absence of comorbidities that could bias associations. Our approach reduces confounding and strengthens internal validity, but limits generalizability and may attenuate age-related differences, highlighting the need for future studies including individuals with diverse health conditions. As mentioned earlier, sex was included as covariate in all analyses, but our sample predominantly consisted of men in the younger subsample and of mainly women in the older subsample, so potential sex differences could not be properly studied here. The sex difference in the relationship between PRS for PD and REM duration that we report in the late-midlife group has, therefore, to be taken with caution. Yet a qualitative consideration of the data collected in women, do not indicate sex difference in our analyses of interest in the younger group. This warrants future investigation including sample balances for sexes, because women present different sleep characteristics and difference in the age-related changes in sleep,[43,44] in addition to the fact that they are less prone to PD.[45]

Although 15% of PD patients have a positive family history, and 5 to 10% of cases follow a Mendelian inheritance pattern, the etiology of PD is multifactorial. It is strongly influenced by environmental factors, with age being the most important risk factor.[3] We, therefore, emphasize that a PRS for PD is not intended for individual prediction. Instead, PRS are used to link the underlying biology of the disease—because polygenic risk is inherently biology-grounded—to relevant phenotypes, including that observed in young adults (or even earlier). Accordingly, we present compelling evidence of an early association between REM sleep and PD-related biology, warranting future investigations to provide the functional understanding of the brain mechanism at stake.

Despite ongoing development of potential neuroprotective agents such as GLP-1 agonists, calcium channel blockers, and urate, their efficacy in modifying disease progression remains unproven.[5] We argue that the detection of early association between REM sleep and PD through PRS could improve the early prediction of PD risk and provide novel intervention targets. However, because PRS is a risk indicator, a longitudinal study showing that REM sleep changes in at risk individuals in association with onset of PD symptoms later in life would be a necessary validation step. The sleep-based interventions could take the form of cognitive behavioral therapy, light therapy, LC stimulation,[46] or pharmacological approaches targeting dopamine or norepinephrine modulation[47] and would need to be tested in large scale interventional studies. Studies show, for instance, that rotigotine, a transdermal dopamine agonist increases REM sleep stability,[48] however, whether it bears positive outcomes for PD is not known.

In conclusion, our analysis involving the detailed electrophysiological phenotyping of a relatively large sample size of 518 healthy individuals showed that PRS for PD is related to REM sleep metrics, specifically its duration and theta energy. The relationship between PRS and sleep switches from positive to negative across younger and late-midlife groups. Our findings suggest that the association between PRS and quantitative REM sleep metrics in late-midlife group is moderated by sex, which may be related to the sex-effects in PD prevalence.[2] Quantitative sleep measures could help in the early detection of the underlying neurodegenerative process leading to several neurological diseases including PD, 2 to 5 decades before typical symptom onset. The early identification of at-risk individuals for developing PD would allow evaluation of possible sleep targeted therapies as well as several neuroprotective agents.

Patients and Methods

Participants

The study sample comprised of 538 (age: 28.09 ± 14.1 years, 104 females) healthy Caucasian participants recruited from the local French-speaking community as part of seven different multi-modal cross-sectional studies. One study contributed to most of the younger sample and included 359 young men to maximize genetic uniformity in what was originally a genetic study.[19] Remaining data of the younger sample (n = 92; 45 women) was collected over five different studies.[49–53] In contrast, data from late middle-age individuals (n = 87; 59 women) were collected as part of a single study.[18] All studies collected quantitative sleep parameters and blood samples to assess PRS for PD (see Fig 1). Participants with poor subjective sleep quality, daytime sleepiness, sleep disorders (including significant sleep apnea, parasomnia, RBD, and RSWA), addiction, cognitive impairment, or taking any medications impacting the Central Nervous System (CNS) were excluded. Further details are provided in Data S1.

The study procedures were approved by the Ethics Committee of the Faculty of Medicine (University of Liège, Belgium). All participants gave their written signed informed consent before their participation in the study and received financial compensation. The study was conducted in accordance with the World Medical Association International Code of Medical Ethics (Declaration of Helsinki) for experiments involving humans.

Of 538 (451 young and 87 old), 14 participants were excluded because of incomplete baseline data, 14 because of lack of genetic data, and six outliers with ±5 standard deviation (SD) resulting in a final sample of 518 (433 young and 85 old) participants. The characteristics of the final participant subsample are reported in Table 1.

Sleep Protocol, EEG Acquisitions, and Processing

The in-lab EEG recordings of sleep collected across seven studies[17,18,49–53] included baseline EEG of night-time sleep at habitual sleep times following at least 1 week of regular sleep–wake schedules monitored by actigraphy. More details (in brief) are provided in Data S1.

Sleep stages were scored in 30-second epochs using a validated automated algorithm (ASEEGA; PHYSIP, Paris, France),[54] in accordance with the 2017 American Academy of Sleep Medicine (AASM) scoring criteria (version 2.4). An automatic artefact and arousal detection algorithm with adaptative thresholds[55] was further applied, and artefact and arousal periods were excluded from subsequent analyses. Power spectrum was computed for each channel using a Fourier transform on successive 4-second bins, overlapping by 2 seconds, resulting in a 0.25Hz frequency resolution. The night was divided into 30-minute windows, from sleep onset, defined as the first NREM2 (N2) stage epoch, until lights-on. Averaged power was computed per 30-minute bins, adjusting for the proportion of rejected data, and subsequently aggregated in a sum separately for REM and NREM sleep.[56] Therefore, we computed SWE (cumulated power in the delta frequency band during N2 and N3 sleep stages, an accepted measure of sleep need),[56] and similar to that we computed the cumulated theta (4–8Hz) power in REM sleep. We, then, computed the cumulated power over the remaining EEG bands, separately for NREM and REM sleep: alpha (8–12Hz), sigma (12–16Hz), beta (16–25Hz), theta (4–8Hz), and delta (0.5–4Hz) bands. As the frontal regions are most sensitive to sleep–wake history,[56] we considered only the frontal electrodes (mean over F3, Fz, and F4), as well as to facilitate interpretation of future large-scale studies using headband EEG, often restricted to frontal electrodes.

Our analyses focused on four sleep metrics to limit issues of multiple comparisons while spanning the most important aspects of REM sleep EEG: (1) REM duration, (2) REM latency, (3) number of arousals during REM sleep, and (4) cumulated theta power during REM sleep. To ascertain specificity of findings we also considered (1) REM percentage, which reflect the overall architecture of sleep rather than only the duration of REM; other frequency band of the EEG during REM; that is, (2) REM alpha energy; (3) REM sigma energy; as well as (4) REM delta energy, because the definition of REM frequencies during REM varies across publication; and finally

(5) SWE during NREM sleep, the dominant oscillatory mode of NREM sleep, considered to be tightly related to the need for sleep.[56]

Genotyping, Quality Control, and Imputation

The blood samples or buccal swabs were collected and stored at −20°C within a few hours until DNA extraction. The genotyping was performed at different time points using the Illumina Infinium OmniExpress-24 BeadChip arrays (Illumina, San Diego, CA) based on Human Build 37 (GRCh37) at Genomics platform of Liège GIGA institute. All the study participants were of European ancestry. Established quality control (QC) procedure was performed using PLINK[57] (http://zzz.bwh.harvard.edu/plink/). In brief, the SNPs were excluded as follows: >10% missing genotypes, <95% call rate, minor allele frequency (MAF) below 0.01, out of Hardy–Weinberg equilibrium (p-value $<10^{-4}$ for the Hardy–Weinberg test). SNPs on 23rd chromosome as well as ambiguous SNPs (A–T, T–A, C–G, G–C) were excluded as well. The data was matched for deviation with European ancestry using 1,000 Genomes Project dataset (1KGP, https://www.internationalgenome.org). Imputation was conducted using the Sanger imputation server (https://imputation.sanger.ac.uk/) based on the Haplotype Reference Consortium (r1.1) as reference panel and using EAGLE2 pre-phasing algorithm. The detailed data processing and analysis for young and late-midlife subsample is as described previously in Muto et al[17] and Koshmanova et al.[19] We finally ended with 7,165,614 SNPs.

PRS Calculation

PRS analyses can be used to assess the genetic liability of an individual for a phenotype by calculating the weighted sum of risk allele's effect size identified in GWAS. In the current study, a PRS for PD based on summary statistics from the recent meta-analysis GWAS for PD of European ancestry was calculated for each participant.[21] The standardization and QC of GWAS summary statistics was performed by MungeSumstats, a Bioconductor R package.[58] In the process, the summary statistics was pruned to align reference alleles to build GRCh37, remove multiallelic variants, and adjust weights for the appropriate reference alleles. The PRS was then generated using SBayesR algorithm implemented in GCTB software. The approach assumes that the SNP effects are drawn from mixtures of distributions with the key metrics defining these genetic architectures estimated through Bayesian frameworks. To derive PRSs from GWAS effect estimates of SNPs, SBayesR essentially uses Bayesian linear mixed model and the reference linkage disequilibrium (LD) correlation matrix. In our analysis, we used banded LD matrix, derived from approximately 1.1 million HapMap3 SNPs in 50,000 unrelated United Kingdom Biobank participants of European ancestry, to improve prediction accuracy as recommended by the authors of GCTB. Applying SBayesR with default parameters to GWAS summary statistics, we obtained updated effect sizes for 1,104,064 SNPs, which were then used to calculate the PRS. We used p-value thresholding through PLINK to include only the SNPs reaching stringent GWAS significance (p-value $<10^{-8}$) to restrict the number of genetic markers. This stringent threshold was pre-specified as our main analytic approach. Analyses at alternative thresholds were conducted to examine the stability of associations under less conservative variant inclusion criteria.

Height as a Negative Control

Based on the current available literature on sleep biology, we assumed absence of any a priori association between the sleep phenotypes and a genetic liability for height. Therefore, we conducted an analysis of polygenic scores estimated for height as a negative control, performing the same GAMLSS analyses as we did for liability to PD.

Statistical Analysis

All analysis was conducted within the R environment (version 4.1.3) (R Development Core Team, 2017). We used GAMLSS[24] to individually assess the associations between four sleep metrics of interests (REM duration, theta in REM, REM latency, and number of arousals in REM) as a dependent variable and the PRS values for PD as an independent variable. GAMLSS offers a wide variety of family of distributions for model fitting[59] and are considered better than GLM or GAM approaches (Fig S6). In our analysis, only the location parameter (μ) is modeled as a function of the covariates. The estimates (β) and confidence interval (CI) are reported in log scale.

Individual values in the dataset were considered outliers if >5 SD from the mean and excluded from analyses. For fitting GAMLSS models, family was selected based on data distribution using fitDist function. Further, models were selected based on the goodness-of-fit values among GAMLSS models and based on the Q–Q plot. Sex, BMI, TST, or REM duration were included as covariates. Before the GAMLSS analysis, influential outliers were also screened using worm plot, a detrended Q–Q plot, which is helpful for checking model fit and comparing the fit of different models. We have provided a representational model fitting diagnostic plot as a Supporting Information figure (Fig S6). Benjamini and Hochberg false discovery rate (FDR) correction was applied to the four pre-specified primary sleep metrics. Analyses of additional sleep metrics and alternative PRS thresholds were performed as

exploratory robustness checks. These supplementary results are, therefore, interpreted with caution and without further multiple testing corrections, because their role is to support the consistency of the primary findings. Sleep metrics were standardized using a Z-transformation for plots.

We computed a priori sensitivity analysis to get an indication of the minimum detectable effect size in our main analyses given our sample size. Based on G*Power 3 (version 3.1.9.4)[60] (https://puneet-talwar.shinyapps.io/PosthocPowerShiny/) taking into account a power of 0.8, an error rate alpha of 0.0125 (corrected for 4 tests), a sample size of 518 allowed us to detect small effect sizes f2 > 0.036 (CI: 0.018–0.09; R^2 > 0.035, R^2 CI: 0.018–0.082) within a linear multiple regression framework including two tested predictor (PRS, age) and four other covariates (sex, BMI, TST, or REM duration). Prior sensitivity analysis for younger and late-midlife subgroups is provided in the Supporting Information.

Acknowledgments

This work is supported by the EU Joint Programme Neurodegenerative Disease Research (JPND) IRONSLEEP project (FNRS reference: PINT-MULTI R.8011.21 to P.T.); the Fonds de la Recherche Scientifique(FRS)-FNRS-Belgium to N.M., F.C., C.P. and C. Bastin, and G.V.; the Wallonia-Brussels Federation (Actions de Recherche Concertées [ARC]-09/14-03,17/27-09); WELBIO/Walloon Excellence in Life Sciences and Biotechnology Grant (WELBIOCR-2010-06E); FNRS-Belgium (FRS-FNRS, F.4513.17 and T.0242.19, T.0238.23, J. 0222.20, and 3.4516.11); Fondation Recherche Alzheimer (SAO-FRA 2019/0025,2022/0014); University of Liege (ULiege); Fondation Simone et Pierre Clerdent; European Regional Development Fund (Radiomed project); Fonds Leon Fredericq; and EU JPND program (IRONSLEEP project-PINT-MULTI R.8011.21). We also thank S. Chellappa, A. Claes, C. Hagelstein, G. Hammad, B. Herbillon, P. Hawotte, M. Jaspar, S. Laloux, E. Lambot, B. Lauricella, A. Luxen, J. Ly, C. Meyer, and E. Salmon for their help over the different steps of the study. This work was conducted at the GIGA-In Vivo Imaging platform of ULiège, Belgium.

Author Contributions

P.T., P.M., and G.V. contributed to the conception and design of the study; P.T., G.V., N.M., E.K., V.M., A.G., C.D., and C.P. contributed to the acquisition and analysis of data; P.T., P.M., G.V., M.Z., F.C., C. Berthomier, and C. Bastin contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

C. Berthomier is an owner of Physip, the company that analyzed the EEG data. This ownership and the collaboration had no impact on the design, data acquisition, results, and interpretations of the findings. The other authors declare that no competing interests exist.

Data Availability

The data and analysis scripts supporting the results included in this manuscript are publicly available via https://gitlab.uliege.be/CyclotronResearchCentre/Public/fasst/pd_prs_and_sleep. The following shiny app developed by P.T. (https://puneet-talwar.shinyapps.io/GAMLSSToolbox/) was also used for the GAMLSS analysis. We used MATLAB scripts for EEG and magnetic resonance imaging data processing, while we used R studio for statistical analyses. Researchers willing to access the raw data should send a request to the corresponding author (G.V.). Data sharing will require evaluation of the request by the local research ethics board and the signature of a data transfer agreement.

References

1. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. Lancet 2020;396:1204–1222.
2. Ben-Shlomo Y, Darweesh S, Llibre-Guerra J, et al. The epidemiology of Parkinson's disease. Lancet 2024;403:283–292.
3. Bloem BR, Okun MS, Klein C. Parkinson's disease. Lancet 2021;397:2284–2303.
4. Koeglsperger T, Rumpf SL, Schliesser P, et al. Neuropathology of incidental Lewy body & prodromal Parkinson's disease. Mol Neurodegener 2023;18:32.
5. Hung AY, Schwarzschild MA. Approaches to disease modification for Parkinson's disease: clinical trials and lessons learned. Neurotherapeutics 2020;17:1393–1405.
6. Al-Qassabi A, Fereshtehnejad SM, Postuma RB. Sleep disturbances in the prodromal stage of Parkinson disease. Curr Treat Options Neurol 2017;19:22.
7. Scammell TE, Arrigoni E, Lipton JO. Neural circuitry of wakefulness and sleep. Neuron 2017;93:747–765.
8. Sohail S, Yu L, Schneider JA, et al. Sleep fragmentation and Parkinson's disease pathology in older adults without Parkinson's disease. Mov Disord 2017;32:1729–1737.
9. Van Egroo M, Narbutas J, Chylinski D, et al. Sleep–wake regulation and the hallmarks of the pathogenesis of Alzheimer's disease. Sleep 2019;42:zsz017.
10. Mestre H, Mori Y, Nedergaard M. The Brain's glymphatic system: current controversies. Trends Neurosci 2020;43:458–466.
11. Koch S, Laabs BH, Kasten M, et al. Validity and prognostic value of a polygenic risk score for Parkinson's disease. Genes 2021;12:1859.
12. Dehestani M, Liu H, Gasser T. Polygenic risk scores contribute to personalized medicine of Parkinson's disease. J Personalized Med 2021;11:1030.

13. Cao Z, Hernandez DG, Li C, et al. Polygenic risk score for Parkinson's disease and olfaction among middle-aged to older women. Parkinsonism Relat Disord 2023;115:105815.

14. Diaz-Torres S, Lee SS, Ogonowski NS, et al. Macular structural integrity estimates are associated with Parkinson's disease genetic risk. Acta Neuropathol Commun 2024;2:130.

15. Maraki MI, Hatzimanolis A, Mourtzi N, et al. Association of the Polygenic Risk Score with the probability of prodromal Parkinson's disease in older adults. Front Mol Neurosci 2021;14:739571.

16. Wang YQ, Liu WY, Li L, et al. Neural circuitry underlying REM sleep: a review of the literature and current concepts. Prog Neurobiol 2021;204:102106.

17. Muto V, Koshmanova E, Ghaemmaghami P, et al. Alzheimer's disease genetic risk and sleep phenotypes in healthy young men: association with more slow waves and daytime sleepiness. Sleep 2021; 44:zsaa137.

18. Chylinski D, Narbutas J, Balteau E, et al. Frontal grey matter microstructure is associated with sleep slow waves characteristics in late midlife. Sleep 2022;45:zsac178.

19. Koshmanova E, Muto V, Chylinski D, et al. Genetic risk for insomnia is associated with objective sleep measures in young and healthy good sleepers. Neurobiol Dis 2022;175:105924.

20. Riemann D, Spiegelhalder K, Nissen C, et al. REM sleep instability--a new pathway for insomnia? Pharmacopsychiatry 2012;45:167–176.

21. Nalls MA, Blauwendraat C, Vallerga CL, et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet Neurol 2019;18:1091–1102.

22. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep 2004;27:1255–1273.

23. Moraes W, Piovezan R, Poyares D, et al. Effects of aging on sleep structure throughout adulthood: a population-based study. Sleep Med 2014;15:401–409.

24. Stasinopoulos MD, Rigby RA, Heller GZ, et al. *Flexible regression and smoothing: using GAMLSS in R*. United States: CRC Press, 2017.

25. Winer JR, Lok R, Weed L, et al. Impaired 24-h activity patterns are associated with an increased risk of Alzheimer's disease, Parkinson's disease, and cognitive decline. Alzheimers Res Ther 2024;16:35.

26. Kalinderi K, Papaliagkas V, Fidani L. The genetic landscape of sleep disorders in Parkinson's disease. Diagnostics (Basel) 2024;14:106.

27. Peever J, Fuller PM. The biology of REM sleep. Curr Biol 2017;27: R1237–R1248.

28. Breen DP, Vuono R, Nawarathna U, et al. Sleep and circadian rhythm regulation in early Parkinson disease. JAMA Neurol 2014;71: 589–595.

29. Otaiku AI. Association of sleep abnormalities in older adults with risk of developing Parkinson's disease. Sleep 2022;45:zsac206.

30. Memon AA, Catiul C, Irwin Z, et al. Quantitative sleep electroencephalogram and cognitive performance in Parkinson's disease with and without rapid eye movement sleep behavior disorder. Front Neurol 2023;14:1223974.

31. Wetter TC, Brunner H, Hogl B, et al. Increased alpha activity in REM sleep in de novo patients with Parkinson's disease. Mov Disord 2001;16:928–933.

32. Maquet P. Sleep function(s) and cerebral metabolism. Behav Brain Res 1995;69:75–83.

33. Zucca FA, Segura-Aguilar J, Ferrari E, et al. Interactions of iron, dopamine and neuromelanin pathways in brain aging and Parkinson's disease. Prog Neurobiol 2017;155:96–119.

34. Osorio-Forero A, Foustoukos G, Cardis R, et al. Infraslow noradrenergic locus coeruleus activity fluctuations are gatekeepers of the NREM-REM sleep cycle. Nat Neurosci 2025;28:84-96.

35. Ehrminger M, Latimier A, Pyatigorskaya N, et al. The coeruleus/subcoeruleus complex in idiopathic rapid eye movement sleep behaviour disorder. Brain 2016;139:1180–1188.

36. Lima MM. Sleep disturbances in Parkinson's disease: the contribution of dopamine in REM sleep regulation. Sleep Med Rev 2013;17:367–375.

37. Takakusaki K, Saitoh K, Harada H, et al. Evidence for a role of basal ganglia in the regulation of rapid eye movement sleep by electrical and chemical stimulation for the pedunculopontine tegmental nucleus and the substantia nigra pars reticulata in decerebrate cats. Neuroscience 2004;124:207–220.

38. Braak H, Del Tredici K, Rub U, et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24: 197–211.

39. Sakata M, Sei H, Toida K, et al. Mesolimbic dopaminergic system is involved in diurnal blood pressure regulation. Brain Res 2002;928: 194–201.

40. Buzsaki G. Hippocampal sharp wave-ripple: a cognitive biomarker for episodic memory and planning. Hippocampus 2015;25:1073–1188.

41. Liu AA, Henin S, Abbaspoor S, et al. A consensus statement on detection of hippocampal sharp wave ripples and differentiation from other fast oscillations. Nat Commun 2022;13:6000.

42. Sei H, Ikemoto K, Arai R, Morita Y. Injection of 6-hydroxydopamine into the ventral tegmental area suppresses the increase in arterial pressure during REM sleep in the rat. Sleep Res Online: SRO 1999;2:1–6.

43. Li J, Vitiello MV, Gooneratne NS. Sleep in Normal Aging. Sleep Med Clin 2018;13:1–11.

44. Eggert T, Dorn H, Danker-Hopfe H. Nocturnal brain activity differs with age and sex: comparisons of sleep EEG power spectra between young and elderly men, and between 60-80-year-old men and women. Nat Sci Sleep 2021;13:1611–1630.

45. Cerri S, Mus L, Blandini F. Parkinson's disease in women and men: What's the difference? J Parkinsons Dis 2019;9:501–515.

46. Rorabaugh JM, Chalermpalanupap T, Botz-Zapp CA, et al. Chemogenetic locus coeruleus activation restores reversal learning in a rat model of Alzheimer's disease. Brain: J Neurol 2017;140: 3023–3038.

47. Phillips C, Fahimi A, Das D, et al. Noradrenergic system in down syndrome and Alzheimer's disease a target for therapy. Curr Alzheimer Res 2016;13:68–83.

48. Pierantozzi M, Placidi F, Liguori C, et al. Rotigotine may improve sleep architecture in Parkinson's disease: a double-blind, randomized, placebo-controlled polysomnographic study. Sleep Med 2016; 21:140–144.

49. Vandewalle G, Archer SN, Wuillaume C, et al. Functional magnetic resonance imaging-assessed brain responses during an executive task depend on interaction of sleep homeostasis, circadian phase, and PER3 genotype. J Neurosci 2009;29:7948–7956.

50. Ly JQM, Gaggioni G, Chellappa SL, et al. Circadian regulation of human cortical excitability. Nat Commun 2016;7:11828.

51. Muto V, Jaspar M, Meyer C, et al. Local modulation of human brain responses by circadian rhythmicity and sleep debt. Science 2016; 353:687–690.

52. Mascetti L, Foret A, Schrouff J, et al. Concurrent synaptic and systems memory consolidation during sleep. J Neurosci 2013;33: 10182–10190.

53. Gaggioni G, Ly JQM, Muto V, et al. Age-related decrease in cortical excitability circadian variations during sleep loss and its links with cognition. Neurobiol Aging 2019;78:52–63.

54. Berthomier C, Muto V, Schmidt C, et al. Exploring scoring methods for research studies: accuracy and variability of visual and automated sleep scoring. J Sleep Res 2020;29:e12994.

55. Chylinski D, Rudzik F, Coppieters TWD, et al. Validation of an automatic arousal detection algorithm for whole-night sleep EEG recordings. Clocks Sleep 2020;2:258–272.

56. Dijk DJ, Landolt HP. Sleep Physiology, Circadian Rhythms, Waking Performance and the Development of Sleep–Wake Therapeutics. *Handb Exp Pharmacol*. Vol 253. Germany: Springer International Publishing, 2019:441-481.

57. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007;81:559–575.

58. Murphy AE, Schilder BM, Skene NG. MungeSumstats: a Bioconductor package for the standardization and quality control of many GWAS summary statistics. Bioinformatics 2021;37:4593–4596.

59. Rigby RA, Stasinopoulos MD, Heller GZ, De Bastiani F. *Distributions for modeling location, scale, and shape: using GAMLSS in R*. United States: Chapman and Hall/CRC, 2019.

60. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*power 3.1: tests for correlation and regression analyses. Behav Res Methods 2009;41:1149–1160.